Rejection under 35 U.S.C. §103(a)

The Examiner maintained the rejection of claims 1 and 3-10 as allegedly unpatentable over Cymbalista '454 as taken in view of Hershenson '605 and Rideout '232.

Applicants are filing concurrently an Appeal Brief that specifically addresses this rejection.

In view of the foregoing remarks and amendments, applicants respectfully request reconsideration and withdrawal of all objections and rejections set forth in the September 11, 1998 Office Action. Applicants maintain that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully requested. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on April 12, 1999:

Charles C. Achkar

Name of applicant, assignee or Registered Representative

Charles Achkar

Signature

April 12, 1999

Date of Signature

EAM/CCA:lac

Respectfully submitted,

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IFN-β LIQUID FORMULATIONS

The present invention relates to liquid formulations of interferon-beta (IFN-β) stabilised with a polyol, a non-reducing sugar or an amino acid. In particular, it relates to liquid formulations containing mannitol. human albumin and acetate buffer.

Interferons (alpha, beta, gamma) are glycoproteins produced in the cells of vertebrates following induction. The most traditional inducers are virus, but also other microbial agents, other natural substances and synthetic compounds have the same behaviour.

Interferon-ß is induced in human fibroblasts, has anti-viral activity. but in the therapy of some tumoral forms, other activities can be exploited together with the anti-viral activity, such as the anti-proliferative cellular activity and immunoregulatory activity.

Production from culture of human fibroblasts, and specifically from recombinant DNA techniques, now allows to obtain industrial quantities of interferon-beta.

It is known that proteins in the purified form are especially susceptible to degradation, even due to the normal activity of atmospheric agents. This peculiarity becomes even more evident for proteins produced according to recombinant DNA techniques.

As a direct consequence of the fact that highly purified proteins are easily subject to denaturization, it becomes desirable to obtain stable formulations which ensure the longest possible life-cycle to the product.

Stabilisation of formulations containing highly purified proteins may be carried out by the addition of one or more excipients which inhibit or delay degradation of the active principle.

Pharmaceutical compositions containing interferon-beta are well known. EP Patent application 89 245 (INTER-YEDA Ltd) describes a lyophilised composition of interferon-beta containing mannitol, human albumin and polyvinylpyrrolidone. the latter as stabilising agent. Also known are pharmaceutical liquid compositions containing other interferons.

International Patent Application WO 89/04177 (GENENTECH - Priority 03/11/87) describes liquid pharmaceutical formulations of gamma-